REMARKS

Before the amendments made herein, claims 1, 7, 17, 22 and 85-92 were pending. New claims 93-99 have been added herewith. Accordingly, after the amendments made herein are entered, claims 1, 7, 17, 22 and 85-99 will be pending.

A Request for Continued Examination (RCE) is being filed concurrently.

A. Regarding the amendments

New claims 93 and 94 are directed to where the molecule of interest specifically binds to P-cadherin. The new claims are supported in the specification, for example, at page 8, lines 14-17.

New claims 95-99 are directed to where P-cadherin modification is detected via specific assays that are disclosed, for example, at page 16, lines 1-15.

Because the amendments made herein are fully supported by the specification, no issue of new matter arises.

B. Regarding written description

The claims are rejected as failing to comply with the written description requirement. Applicants respectfully traverse the rejection.

Data confirming the subject invention

Before addressing the Action's allegations below, Applicants wish to highlight data confirming the disclosure and teaching of the subject invention.

Specifically, two oligonucleotides, which are siRNA molecules, were shown to a) inhibit P-cadherin and b) inhibit hair growth. The sequence of one siRNA molecule is CACACGACCUCAUGUUCACCAUUCA (with a complementary sequence) and the sequence for the other is rGrGrArCrArGrGrCUrGrGUUr (with a complementary sequence).

Applicants attach results regarding the first of these siRNA molecules, which shows that it is a P-cadherin inhibitor. More specifically, the attached chart shows a luciferase reported assay, where P-cadherin captures a certain level of the reporter (see columns 1 and 5 of chart), and the siRNA molecule inhibits P-cadherin, thus allowing more reporter expression (see column 9). Applicants would be happy to submit this data in a declaration if deemed necessary by the Examiner.

Turning to the allegations made, the Action cites: 1) the reasons given on page 3 of the current Action; and 2) the reasons given in item 10 of the previous Action. Applicants will take the allegations made in both sections in logical order:

1. Allegation #1 - The subject specification does not describe a specific method to identify a modulator of P-cadherin.

The previous Action alleges that the subject specification does not describe a specific method to identify a modulator of P-cadherin. Applicants respectfully take issue with this allegation.

Response

Several specific methods are disclosed. The skilled artisan would know how to employ these specific methods to try to identify the target molecules.

As disclosed on page 16 of the specification, "There are numerous [ways] for testing P-Cadherin function. Several assays are known for monitoring P-cadherin function, such as binding β-catenin and/or other cellular skeleton components. These assays include immunoprecipitation of cell extracts with an anti-Pcadherin antibody and immunoblotting of this reaction products to reveal a 116kD band representing P-cadherin as well as three smaller bands corresponding in decreasing size order to α-, β-, γ-catenins; microscopic examination of cell cultures in the presence of anti-E cadherin in which further inhibition of P-cadherin function leads to cell-cell interaction disruption and inhibition of keratinocyte differentiation; inhibition of actin cytoskeleton formation under changing Ca^{++} concentrations in keratinocyte cell-cultures (Lewis, J.E., Jensen, P.J. & Wheelock, M.J *J. Invest. Dermatol.* **102**, 870-877 (1994)). Furthermore, assessing an increase or decrease of P-Cadherin expression is taught in the specification and is well known in the art.

Thus, if a given candidate molecule increases or decreases P-Cadherin function or expression, this change in function or expression can be measured, for example, by the specific ways outlined above.

Furthermore, the specification teaches ways of making anti-P-Cadherin antibodies, including using specific peptides (SEQ ID NOS:40 to 45) that are unique to P-Cadherin as opposed to other cadherins. See specification at page 11-24. The specification also contains further disclosure for making such antibodies. See page 29, line 15 to page 30, line 27.

In addition, the specification discloses several other ways of identifying peptides or proteins that bind with P-Cadherin. See for example the yeast-based two hybrid system (page 32, line 20 to page 33, line 23), the prokaryote two-hybrid system (page 33, line 24 to page 34, line 2) and using a phage display library (page 33, lines 3-11). Other forms of modulators, such as antisense molecules, are also disclosed including specific candidates likely to be inhibitors. See page 16, line 11 to page 17, line 10 and SEQ ID NOS:21-39.

2. Allegation #2 – The broad brush discussion of making and screening for antibodies and antisense molecules does not constitute a disclosure of a representative number of members. No such antibodies or antisense molecules were made or shown to have activity. Only the polpeptide of SEQ ID NOs: 21-39 is disclosed. The specification's general discussion of making and screening for antibodies and antisense molecules constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description of the claims variants.

This is what the current Action alleges. Applicants will response to each part of the allegation.

a. Part 1 - The broad brush discussion of making and screening for antibodies and antisense molecules does not constitute a disclosure of a representative number of members. ... Such does not constitute an adequate written description of the claims' variants.

Response

The current Action alleges that the "broad brush discussion of making and screening for antibodies and antisense molecules does not constitute a disclosure of a representative number of members." The Action later concludes that "such does not constitute an adequate written description of the claims' variants." What are the "members" and "variants" that the Action is referring to? Applicants assume the

Action is alleging that the subject Application is not referring to ways of measuring P-cadherin activity, as several such ways are disclosed, as discussed above.

Accordingly, Applicants assume the Action is referring to "a representative number of members" or "variants" of target molecules. However, this allegation is first and foremost irrelevant, as clearly stated by case law.

While the *Gostelli* case, cited by the examiner in the previous Action, stated that disclosure of two compounds within a subgenus was not enough to describe that subgenus, the claims at issue in that case were directed to **that subgenus**, and not methods of **identifying** compounds within that subgenus, as in the case at hand. Similarly, § 2163 is addressing claims to a genus, and not claims directed to **identifying** compounds within such genus.

This distinction is critical. The law regarding a genus when the claims are not directed to the genus, but rather some other aspect, is completely different. See, for example, *Application of Herschler*, 200 USPQ 711 (CCPA 1979). In *Herschler*, the applicant had discovered that dimethylsulfoxide (DMSO) was useful as a transdermal carrier for physiologically active steroids. The CCPA found that a priority application describing a **single steroid** (dexamethasone 21-phosphate) supported a claim to the **genus of all steroids**, both known and unknown. The court explained that *Herschler*'s claims were not drawn to steroids but to the method of administration of steroids.

Similarly, the subject claims are drawn to methods of identifying certain compounds, not to the compounds themselves.

It is interesting to again note that even unknown steroids were covered in *Herschler*. Similarly, the Applicant's data discussed above and attached herewith is directed to siRNA, a class of molecules that were largely unknown at the time the subject invention was made! Similarly, the luciferase reporter assay used and attached was also not known. It is simply another way of measuring P-cadherin activity. This assay and class of molecules clearly exemplify the invention and attest to the appropriateness of the generic nature of the subject claims.

Even more on point is, for example, U.S. Patent No. 6,998,261. Issued claim 31 of this patent recites as follows:

> 31. A method of determining the gene encoding the target of a biologically active compound comprising the steps of: (A) creating an array of stable haploid populations of yeast cells having at least two selecting markers and a recombinant plasmid wherein: (a) the first marker is a dominant selectable marker wherein said marker is recombinantly inserted into an essential yeast gene rendering that essential gene inactive where the members of the array have different essential genes inactivated; (b) the second marker is a defined haploid-selecting recessive marker; and (c) the recombinant plasmid comprises a functional heterologous gene that complements the essential gene inactivated by the dominant selectable marker; (d) the haploid population is derived from a population of diploid yeast cells having at least two recombinant insertions and transformed by at least one recombinant plasmid where: (i) the first insertion is a dominant selectable marker said marker inserted into an essential yeast gene rendering that essential gene inactive; and, (ii) the second recombinant insertion is a single copy of a dominant counter selectable (sensitive) marker and is allelic to a corresponding haploid-selecting recessive marker in the parental diploid yeast; and, (e) populations within the array are dependent upon different heterologous genes for survival; (B) contacting the array with the biologically active compound in an amount that produces a compound-specific reaction with a population of the array but not with all populations, and, (C) determining the yeast population within the array that is reactive to the compound.

It is absolutely critical to note that there are **zero** specific "biologically active compounds" described in this patent. Indeed, Example 4 of the patent, which describes how this method is performed, is completely prophetic.

The case law and patent cited above makes clear that Applicants need not describe "a representative" number of P-cadherin modulators to comply with the written description requirement. This is because the subject claims are directed to methods of identifying such molecules, and are not directed to the molecules themselves.

b. Part 2 - No such antibodies or antisense molecules were made or shown to have activity. Only the polypeptide of SEQ ID NOs: 21-39 is disclosed.
Response

As discussed above, case law makes clear that this allegation, even if true, is not relevant.

In addition, the allegation is not true.

i. Regarding antisense molecules

SEQ ID NOS: 21-39 are not polypeptides but rather, oligonucleotides. They are disclosed on pages 16-17 of the subject application as follows:

1. GAGAGGTCCACGAGGGAGCCC (74-94) (SEQ ID NO:21)
2. CACGGCTCGGAGGCCGCGCA (131-150) (SEQ ID NO:22)
3. CGCCTCCAAGGTCACTTCAG (171-191) (SEQ ID NO:23)
4. CTAAACAGAGCTGGCTCTTG (251-270) (SEQ ID NO:24)
5. AGTGACCTTCTTTCCTGGAC (311-330) (SEQ ID NO:25)
6. GTTTGGATGGGAAGATCTTC (349-368) (SEQ ID NO:26)
7. CTTGTGTCTTCGTAAGATAC (369-388) (SEQ ID NO:27)
8. CTGGGGGAAGGGACCCTTGC (429-448) (SEQ ID NO:28)
9. CTTCAGCACAAAAGGGGCCT (1308-1027) (SEQ ID NO:29)
10. CAACGACTTTGGAGGGTGGGAC (1391-1412) (SEQ ID NO:30)
11. GTTGTTCCTCACAAACTGCTC (1586-1606) (SEQ ID NO:31)
12. GTGGTGGGAGGGCTTCCATTG (1636-1656) (SEQ ID NO:32)
13 GATCTGACGGGGCTCAGGGAC (1709-1729) (SEQ ID NO:33)
14. CATCTGTGAGCTGGGCCTGG (1807-1826) (SEQ ID NO:34)
15. CCTTCCTCGTTGACCTCTGCC (1846-1866) (SEQ ID NO:35)
16. CTTTGTTGCCATGGTCAGACAG (1931-1952) (SEQ ID NO:36)
17. GCAGCACCAGCAGGAGGAAC (2071-2090) (SEQ ID NO:37)
18. GGTTGGTGCCACGTCATTGCG (2261-2281) (SEQ ID NO:38)
19. GTTGGCTGGCCGAGGACGGTAC (2278-2298) (SEQ ID NO:39)

More specifically, as disclosed on page 16, lines 16-22 of the subject application, "Figures 3a-p present an alignment of human cadherin cDNAs (SEQ ID NOs:11-20). Those regions for which no or low homology exists between P-cadherin and other human cadherins were identified." The specification discloses that the above-cited oligonucleotides are exemplary oligonucleotides capable of specifically binding to P-cadherin gene, pre-messenger RNA or messenger RNA under physiological conditions and hence serve as P-cadherin inhibitors, via inhibiting P-cadherin expression. In view of this disclosure, the skilled artisan clearly can see specific examples of molecules that can be made and tested for activity.

ii. Regarding antibodies

Page 29, lines 3-24 of the specification discloses as follows: According to another embodiment of the present invention, the P-cadherin modulator, or the molecule capable of binding P-cadherin, is an anti-P-cadherin antibody and hence serves as a P-cadherin inhibitor.

Figures 4a-d shows an alignment of the intracellular and extracellular portions of human cadherins. Short sequences of low similarity between P-cadherin and the other human cadherins, especially E-cadherin, were identified. These sequences are used in accordance with the teachings of the present invention to generate antibodies specific to P-cadherin.

The following peptides are thought to have a potential of eliciting antibodies specific to P-cadherin as they share low or no similarity with corresponding sequences of other human cadherins and/or mouse cadherins and were identified as immunogenic by the peptidestructure algorithm from the GCG package:

For the extracellular domain of P-cadherin:

1. VPENGKGPFP (117-124) (SEQ ID NO:40) both immunogenic and not homologous to either mouse P-cadherin or other human cadherins;
2. QEPKDPHDLMFTIHRSTGT (259-277)(SEQ ID NO:41);
3. DNGSPPTTGT (522-531)(SEQ ID NO:42);
4. TDKDLSPHTSPFQAQLTDDSDIY(568-590)(SEQ ID NO:43);
5. DCHGHVETCPGPWKGG (639-654)(SEQ ID NO:44);

For the cytoplasmic domain of P-cadherin:

6. MYRPRPANPDEI(743-754)(SEQ ID NO:45)

Thus, the subject specification is providing extremely specific guidance for the skilled artisan to make anti-P-cadherin antibodies to test for activity.

c. Part 3 - The specification's general discussion of making and screening for antibodies and antisense molecules constitutes an invitation to experiment by trial and error.

Response

Once again, the Action is confusing methods to the genus itself, such as methods directed to treating a condition by using a compound within chemical genus, with methods directed to identifying a compound within that genus.

The subject claims can operate by using trial and error and lead to the identification of compounds that can modulate P-cadherin. This does not take away from the patentability of the invention. If it did, then no method of, for example, high-throughput screening to identify useful compounds would be patentable because such a method **by definition** employs trial and error. Applicants would be happy to provide further examples of issued patents with such method claims, even though such methods require trial and error (and also have minimal or no specific description of the precise compounds sought to be identified, and no disclosure of any active compounds).

In summary, the subject claims are directed to methods of identifying a molecule. Under the law, the written description requirements imposed by the Action are not relevant. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Conclusion

All of the issues raised in the Final Office Action have been addressed and are believed to have been overcome. Accordingly, it is respectfully submitted that all the claims under examination in the subject application are allowable. Therefore, Applicants respectfully request a Notice of Allowance to this effect.

Respectfully submitted,

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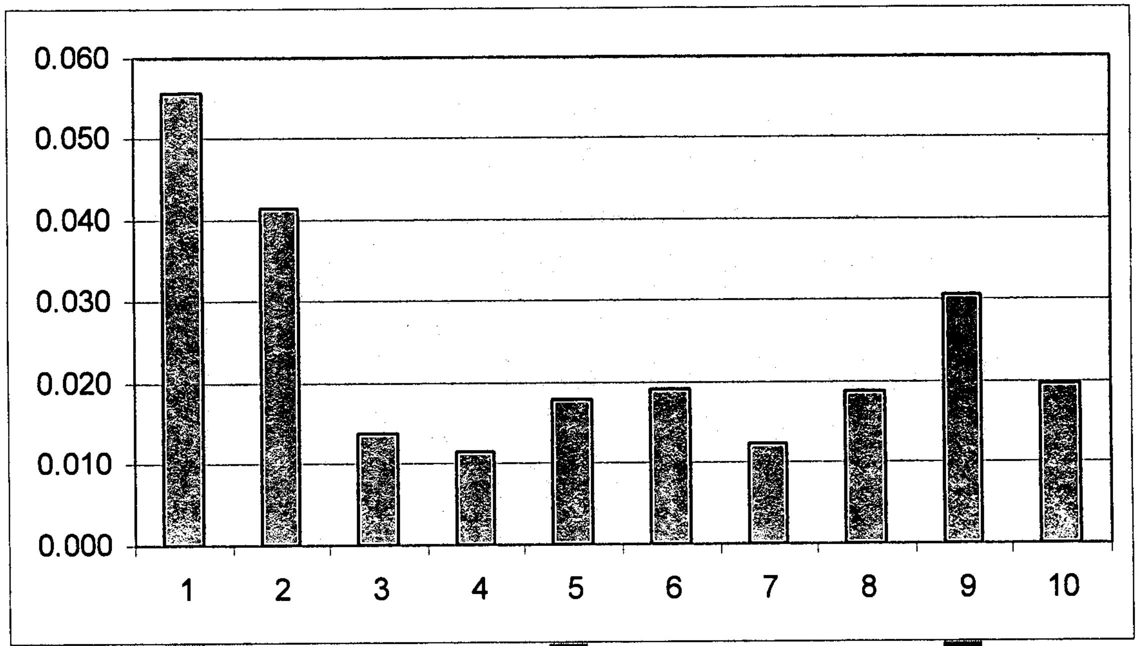
Date: May 6, 2008

Enclosures:

- Request for Continued Examination (RCE)
- Petition for Extension of Time (3 Months)
- Chart



HFz1	+	+	+	+	+	+	+	+	+	+
Wnt 3a	+	+	+	+	+	+	+	+	+	+
pGL3OT	+	+	-	-	+	+	-	-	+	-
pGL3OF	-	-	+	+	-	-	+	+	-	+
Renila	+	+	+	+	+	+	+	+	+	+
P-cadherin	-	-	-	-	+	+	+	+	+	+
pDEST	+	+	+	+	-	-	-	-	-	-
scramble	+	-	+	-	+	-	+	-	-	-
siRNA	-	-	-	-	-	-	-	-	+	+